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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,075	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *11-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/04;03/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I, claims 1-10 in the reply filed on 02/03/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant further elected the species Ang-2. However, the species election is not relevant to the elected invention. Therefore, claims 1-10 are examined for their full-breadth.

Claims 11-49 are withdrawn. Claims 1-49 are pending and claims 1-10 are under examination in the instant office action.

Oath/Declaration

It is noted that the Oath filed 12/23/2003 indicates that Applicant is claiming foreign priority. However, no foreign documents are listed in the oath or provided with the application.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is unclear because it is not clear if the structure encompassed by the claim is intended to encompass a single regulatory element operably linked to both the first and second

nucleic acid or separate regulatory elements operably linked to each of the first and second nucleic acids. As such, claims 6 and 7, which depend from claim 5, are unclear because they require mutually exclusive limitations of the regulatory element of claim 5. If claim 5 is intended to encompass separate regulatory elements operably linked to each nucleic acid, then claims 6 and 7 appear to necessitate that the separate regulatory elements be of the same structure and function. Claims 6 and 7 depend from claim 5.

Claims 6 and 7 recite the limitation "said bioluminescent gene product" in line 2 of each claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 is unclear because it is not known if the term "inducible" encompasses tissue-specific promoters that are induced by tissue-specific transcription factors. The specification defines "regulatory elements" as either constitutive or inducible that may be coupled to additional elements that render cell-type specific or tissue specific expression. It is unclear whether the term "inducible" in claim 7 is directed to promoters that are directly inducible such as the tet promoter or the metallothionein promoter or if it is meant to include tissue and cell-type specific promoters. For the purpose of examination, because tissue-specific promoters are not constitutive, based on this definition as given by the specification, it is assumed that tissue-specific or cell-type specific promoters are inducible. However, clarification is necessary.

Claim 10 recites the limitation "said viral vector" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 10 depends from claim 8, not claim 9.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-6 and 8-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Zakhartchenko et al [September 2001, **BioTechniques**, 31:676-684].

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claims 2-4 limit the gene products to a bioluminescent gene product (claim 2), luciferase (claim 3) and neomycin phosphotransferase (claim 4). Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 6 limits the regulatory element to one that effects constitutive expression. Claims 8-10 require that the polynucleotide be comprised by a vector (claim 8) wherein the vector is a viral vector (claim 9) and wherein the viral vector is a retroviral vector (claim 10).

Zakhartchenko taught a retroviral vector (fulfilling the limitations of claims 8-10), comprising *luc*+ and *neo* genes (fulfilling the limitations of claims 1-4). The *luc*+ gene is operably linked to a constitutive HCMV promoter (fulfilling the limitations of claim 6) and the *neo* gene is operably linked to a constitutive SV40 late promoter (see Figure 1).

Therefore, Zakhartchenko meets the limitations of claims 1-6 and 8-10.

2) Claims 1-5 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilson et al. [March, 2002, IDS].

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claims 2-4 limit the gene products to a bioluminescent gene product (claim 2), luciferase (claim 3) and neomycin phosphotransferase (claim 4). Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 7 limits the regulatory element to one that effects inducible expression.

Wilson taught the pMMTV.luc.neo vector comprising *luc* and *neo* genes wherein the luciferase gene is operably linked to an inducible MMTV LTR promoter (see page 70, col. 2, paragraph 2; Figure 2). *luc* encodes luciferase, which is a bioluminescent protein.

Therefore, Wilson meets the limitations of claims 1-5 and 7.

3) Claims 1-5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Terouanne et al. [2000, **Molecular and Cellular Endocrinology**, 160:39-49].

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claims 2-4 limit the gene products to a bioluminescent gene product (claim 2), luciferase (claim 3) and neomycin phosphotransferase (claim 4). Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 7 limits the regulatory element to one that effects inducible expression.

Terouanne taught a plasmid vector comprising *luc* and *neo* genes. *luc* encodes a bioluminescent protein. The *luc*+ gene is operably linked to an inducible MMTV LTR promoter

(see paragraph bridging paged 40-41). The neo gene is operably linked to an SV40 promoter (page 41, col. 1, lines 3-4).

Therefore, Terouanne meets the limitations of claims 1-5 and 7.

4) Claims 1-6 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Levine et al. [1991, **Gene**, 108:167-174].

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claims 2-4 limit the gene products to a bioluminescent gene product (claim 2), luciferase (claim 3) and neomycin phosphotransferase (claim 4). Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 6 limits the regulatory element to one that effect constitutive expression. Claims 8-10 require that the polynucleotide be comprised by a vector (claim 8) wherein the vector is a viral vector (claim 9) and wherein the viral vector is a retroviral vector (claim 10).

Levine taught two types of retroviral vector (see Figures 1A and 1B). Both vectors comprise *luc* (encoding a bioluminescent protein) and *neo* (encoding a neomycin phosphotransferase) genes. In the first vector, there are two different promoters, the promoter in the 5'LTR of the retrovirus (MMLV, constitutive) and RSV promoter that is operably linked only to *neo*. The second construct comprises only the promoter in the 5'LTR of the retrovirus, which effects expression of both the *luc* and *neo* genes.

Therefore, Levine meets the limitations of claims 1-6 and 8-10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zakhartchenko et al. as applied to claims 1-6 and 8-10 above, and further in view of Yee et al [1987, **PNAS**, 84:5197-5201].

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 7 limits the regulatory element to one that effects inducible expression.

As, set forth above, Zakhartchenko taught a retroviral vector comprising *luc*+ and *neo* genes. The *luc*+ gene is operably linked to a constitutive HCMV promoter and the *neo* gene is

operably linked to a constitutive SV40 late promoter (see Figure 1). Zakhartchenko did not teach use of a regulatory element that effects inducible expression.

However, Yee taught use of SIN viral vectors that have been altered to eliminate many of the LTR elements necessary for viral transcriptional activity. Yee incorporated an inducible metallothionein promoter into the SIN retrovirus, leading to regulatable expression of a reporter gene (paragraph bridging columns at page 5197; paragraph bridging pages 5197-5198; paragraph bridging columns at page 5198).

One of skill in the art at the time of filing would have been motivated to combine the teachings of Zakhartchenko et al. using retroviral vectors to introduce a luciferase reporter gene into cells with the teachings of Yee et al., incorporating an inducible promoter into the vector in place of a constitutive promoter. One of skill in the art would have been motivated to use an inducible promoter over a constitutive promoter for several reasons including the ability to control expression of a reporter gene or other gene of interest, to provide tissue-specific expression in vivo, as well as use of the construct as an indicator of the cellular environment such as the presence of heavy metals (metallothionein) or the presence of transcription factor indicative of various cellular processes.

One of skill in the art at the time of filing would have had a reasonable expectation of success in combining the teachings of Zakhartchenko and Yee because the technology involving use and manipulation of SIN retroviral vectors was highly characterized and a multitude of inducible promoter systems were available.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zakhartchenko et al. as applied to claims 1-6 and 8-10 above, and further in view of Hwang et al [1997, **Journal of Virology**, 71:7128-7131] or Hu [2000, **Pharmacol. Reviews**, 52:493-511].

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 7 limits the regulatory element to one that effects inducible expression.

As set forth above, Zakhartchenko taught a retroviral vector comprising *luc*+ and *neo* genes. The *luc*+ gene is operably linked to a constitutive HCMV promoter and the *neo* gene is operably linked to a constitutive SV40 late promoter (see Figure 1). Zakhartchenko did not teach use of a regulatory element that effects inducible expression.

However, Hwang taught use of SIN viral vectors that have been altered to eliminate and replace the U3 LTR elements necessary for viral transcriptional activity with an inducible tet

promoter in the LTR (paragraph bridging columns at page 7128; Figure 1). Hwang taught that inducible promoters in the LTR lead to effective inducible activity and increase SIN viral titers.

Hu taught that tissue specific regulatory elements can be used to replace the U3 LTR elements in SIN retroviral vectors, conferring tissue-specific (inducible) expression of a reporter gene or other gene of interest (Figure 11; page 506, col. 1, paragraph 2).

One of skill in the art at the time of filing would have been motivated to combine the teachings of Zakhartchenko et al. using retroviral vectors to introduce a luciferase reporter gene into cells with the teachings of Hwang et al. or of Hu incorporating an inducible/tissue specific promoter into the vector in place of the viral LTR promoter. One of skill in the art would have been motivated to use an inducible promoter such as the tet promoter or a cell-type specific promoter over a constitutive promoter, for several reasons including the ability to control expression of a reporter gene or other gene of interest, provide tissue-specific expression in vivo, as well as use of the construct as an indicator of the cellular environment such as the presence of various transcriptional regulators including ions, hormones or proteins.

One of skill in the art at the time of filing would have had a reasonable expectation of success in combining the teachings of Zakhartchenko and Hwang or Hu because the technology involving use and manipulation of SIN retroviral vectors was highly characterized and a multitude of inducible promoter systems were available. Furthermore, Hwang and Hu each taught that inducible promoters effective as replacements for the viral LTR promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

3) Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al. as applied to claims 1-6 and 8-10 above, and further in view of Hwang et al [1997, Journal of Virology, 71:7128-7131] or Hu [2000, Pharmacol. Reviews, 52:493-511].

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is drawn to a polynucleotide comprising a first nucleic acid encoding a light generating gene product and a second nucleic acid encoding a selectable marker that allows for selection in a eukaryotic host. Claim 5 requires a regulatory element be operably linked to said nucleic acids. Claim 7 limits the regulatory element to one that effects inducible expression.

As set froth above, Levine taught two types of retroviral vector (see Figures 1A and 1B). Both vectors comprise *luc* (encoding a bioluminescent protein) and *neo* (encoding a neomycin phosphotransferase) genes. In the first vector, there are two different promoters, the promoter in the 5'LTR of the retrovirus (MMLV, constitutive) and RSV promoter that is operably linked only to *neo*. The second construct comprises only the promoter in the 5'LTR of the retrovirus, which effects expression of both the *luc* and *neo* genes. In both vectors, luciferase expression is drive from the constitutive MMLV promoter. Levine did not teach use of an inducible promoter to drive luciferase expression.

However, Hwang taught use of SIN viral vectors that have been altered to eliminate and replace the U3 LTR elements necessary for viral transcriptional activity with an inducible tet promoter in the LTR (paragraph bridging columns at page 7128; Figure 1). Hwang taught that inducible promoters in the LTR lead to effective inducible activity and increase SIN viral titers.

Hu taught that tissue specific regulatory elements can be used to replace the U3 LTR elements in SIN retroviral vectors, conferring tissue-specific (inducible) expression of a reporter gene or other gene of interest (Figure 11; page 506, col. 1, paragraph 2).

One of skill in the art at the time of filing would have been motivated to combine the teachings of Levine et al. using retroviral vectors to introduce a luciferase reporter gene into cells with the teachings of Hwang et al. or of Hu incorporating an inducible/tissue specific promoter into the vector in place of the viral LTR promoter. One of skill in the art would have been motivated to use an inducible promoter such as the tet promoter or a cell-type specific promoter over a constitutive promoter, for several reasons including the ability to control expression of a reporter gene or other gene of interest, provide tissue-specific expression in vivo, as well as use of the construct as an indicator of the cellular environment such as the presence of various transcriptional regulators including ions, hormones or proteins.

One of skill in the art at the time of filing would have had a reasonable expectation of success in combining the teachings of Levine and Hwang or Hu because the technology involving use and manipulation of retroviral vectors to replace the viral transcriptional regulatory U3 region was highly characterized and a multitude of inducible promoter systems were available. Furthermore, Hwang and Hu each taught that inducible promoters effective as replacements for the viral LTR promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632